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BRANCH RECOMMENDATION

Gastrointestinal and hepatic manifestations of COVID-19 in children

Manifestaciones gastrointestinales y hepáticas de COVID-19 en niños

Mónica Villanueva Ch.[a], Rossana Faundez H.[b], Marcela Godoy[c]

[a]Unidad de Gastroenterología Pediátrica Clínica Alemana de Santiago. Unidad de Gastroenterología Pediátrica Hospital Clínico San Juan de Dios. Facultad de Medicina Universidad de Chile. Santiago, Chile
[b]Unidad de Gastroenterología Pediátrica Hospital Clínico San Juan de Dios. Facultad de Medicina Universidad de Chile. Unidad de Gastroenterología Pediátrica Clínica Santa María. Santiago, Chile
[c] Unidad de Gastroenterología Pediátrica. Servicio de Pediatría Hospital Clínico San Borja Arriarán. Rama de Gastroenterología de la Sociedad Chilena de Pediatría. Santiago, Chile

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What do we know about the subject matter of this study?

SARS-CoV-2 is a respiratory pathogen that may also affects the digestive system. About 10% of children develop diarrhea and vomiting. Asymptomatic patients, especially children, can transmit the disease. Elevation of transaminase is detected in 40-60% of patients with severe disease, and 18-25% of those who are asymptomatic or have mild disease.

What does this study contribute to what is already known?

This study alerts us about the gastrointestinal and hepatic manifestations that have been described in COVID-19 (+) patients, allowing us to increase the rate of suspicion, make an early diagnosis, and recognize complications of the disease.

Abstract

SARS-CoV-2 is a high environmental stable virus. It is predominantly a respiratory pathogen that also affects the gastrointestinal tract. The ACE 2 receptor is the main receptor of SARS-CoV-2, with evidence of its high presence in the intestine, colon and cholangiocytes, and, in smaller proportion, in hepatocytes. SARS-CoV-2 has a gastrointestinal tropism that explains digestive symptoms and viral spread in stools. The characteristics of this virus include the S (Spike) protein that binds very stably to the ACE-2 receptor and, at the same time, SARS-CoV-2 produces dysbiosis and alterations in the gut-lung axis. It produces a clear T-cell response and a cytokines storm in the intestine and liver that would produce inflammatory bowel damage. Intestinal manifestations by order of frequency are loss of appetite, diarrhea, nausea and vomiting, and abdominal pain, where the latter could be a severity marker. In children, diarrhea is the most frequent symptom, usually mild and self-limiting. In the liver, hypertransaminasemia occurs in severe patients ranging from 40 to 60%. SARS-CoV-2 can remain in stools longer than in respiratory secretions, which would influence the spread of disease. This article highlights the importance of an early diagnosis of gastrointestinal and hepatic manifestations, increase the index of suspicion, make a timely diagnosis, and recognize eventual complications of the disease. The potential oral-fecal route of transmission may influence the disease spread. Recognizing this finding is important to define isolation.

Keywords:
SARS-CoV-2;
Diarrhea;
Hypertransaminasemia;
Fecal-Oral
Transmission

Correspondence:
Mónica Villanueva
mvillanuevac@alemana.cl

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Introduction

SARS-CoV-2 is the seventh coronavirus identified capable of infecting humans[1]. In 2019, it emerged as a new beta coronavirus[2]. It is a single-stranded RNA virus whose intermediate transmitter has not been identified yet[1], is highly contagious, stable in the environment, and is mainly transmitted between humans[3]. Its genetic characteristics show that 89% of its nuclear sequence is similar to Bat SARS-like-CoVZXC21 and 82% to SARS-CoV[4]. It can affect people of all ages with a high rate of infectivity, however, children may be less susceptible[1].

As of 14th July 2020, SARS-CoV-2 has infected 13,284,292 people globally, resulting in 577,843 deaths[5]. Out of them, there are 319,493 infected and 7,069 dead in Chile, and of these, 4.8% are children under the age of 15[6]. There are series describing a prevalence of up to 24.8% in the pediatric population[1], where the most frequently affected are children with heart disease, under 3 years of age[2].

Of the adult population14% presents severe manifestations and 5% are critical (respiratory failure, septic shock, multiple organ failure), reaching a mortality rate of 2.3%[7]. In another cohort of patients, 6% of children developed severe disease compared with 18.5% of adults[8]. In Chile, as of 12 July 2020, 244 pediatric patients have been discharged from intensive care units (240 alive and 4 deceased), 62/244 required ventilatory support, and 63/244 presented PIMS or hypercoagulability. Thirty-nine patients aged under 20 years of age died (14 confirmed and 25 suspected COVID-19 infection)[6].

Although SARS-CoV-2 is mainly a respiratory pathogen, it also affects the gastrointestinal tract. About 10% of children with infection develop diarrhea and vomiting. There are reports of isolated diarrhea before cough and fever. Prolonged positive SARS-CoV-2 in the stool increases the possibility of fecal-oral transmission. Asymptomatic individuals, especially children, may behave as transmitters of the disease due to the lower suspicion rate and therefore lower chance of detection[7].

On the other hand, patients with severe SARS-CoV-2 disease present a increase up to 40-60% of transaminases levels compared with those that are asymptomatic or those with mild disease, where it rises in 18%-25% of cases. In addition, some cases of acute liver failure have been reported[9-11].

The objective of this publication is to alert about the gastrointestinal and hepatic manifestations that have been reported in COVID-19 (+) patients in order to increase the suspicion rate, make timely diagnosis, and recognize possible complications of the disease.

Pathophysiology of gastrointestinal and hepatic involvement

SARS-CoV-2 is primarily a respiratory pathogen that may cause severe acute respiratory syndrome, but it is also a virus that can affect the gastrointestinal tract (GI tract).

The fact that a non-enveloped virus can survive exposure to low gastric pH and the detergent effect of bile salts, could be due to characteristics shared with other coronaviruses such as extensively glycosylation of spike (S) protein, its intrinsic evolution at low pH and in the presence of digestive enzymes, and also to the formation of a compound with mucins complex. These conditions could also explain its great stability in the environment[3].

Several explanations for intestinal involvement caused by SARS-CoV-2 are possible. First, the angiotensin-converting enzyme receptor 2 (ACE2) has been established as a probable cellular receptor for SARS-CoV-2[12]. This receptor is associated with an X-linked gene producing sexual dimorphism in the liver and gastrointestinal tract, causing differences in its expression between men and women due to the difference of genetic the expression of ACE2. This characteristic would contribute to more severe clinical manifestation in males, smokers, and COPD patients who have greater expression of this enzyme[3,13].

As in the respiratory mucosa (in alveolar type II cells), ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) are co-expressed in the gastrointestinal tract, specifically in glandular cells of the esophagus and the apical cell surface of the ileum and colon[3,9,10]. They are also expressed in monocytes, macrophages, and endothelial cells[9]. Both proteins are key to the physiopathology of the disease. Their co-expression in the same cell is essential to allow virus entry[9].

SARS-CoV-2 encodes 4 structural proteins, the S-protein (spike protein), the E-protein (envelope), the M-protein (membrane), and the N-protein (nucleocapsid). The SARS-CoV-2 S-protein has a high affinity for ACE2 and is mainly responsible for viral entry[1,3,14]. During viral maturation, the S-protein is glycosylated and divided into two parts, S1 and S2. The S1 protein is spherical and its main function is the recognition and binding of the virus to the host cells. The S2-protein can promote the fusion of the virus with the cell membrane[14]. Given these characteristics, SARS-CoV-2 has a high efficiency when binding to cells which could explain its high percentage of transmission[10].

After virus entry, virus-specific RNA and proteins are synthesized in the cell cytoplasm to produce new virions, which are then released into the GI tract[10].

Therefore, SARS-CoV-2 has gastrointestinal tro-

pism which may that explain the digestive symptoms and viral spread in stools[9] SARS-CoV-2-associated diarrhea may be related to proteins or toxins produced during viral replication[15], or possibly intestinal inflammation mediated by T-lymphocyte may occur.

Gut microbiota has an important role, it has been proposed that SARS-CoV-2 would cause dysbiosis because, under physiological conditions, the ACE2 receptor in the intestine would serve for the expression of the amino acid transporter B^0AT1. This ACE2-B^0AT1 receptor association allows entry of tryptophan into the enterocyte. This tryptophan is regulated through mTOR, which is a pathway for activation of antimicrobial peptide secretion that significantly defines the composition of the intestinal microbiota. When this ACE2 receptor is occupied by SARS-CoV-2, tryptophan cannot be metabolized efficiently, producing aberrant secretion of antimicrobial peptides and, consequently, a dysbiosis that confers susceptibility to small bowel inflammation[16].

Intestinal and respiratory microbiota develop simultaneously after birth where, in healthy individuals, these colonies are predominantly phylum, bacteroidetes, and firmicutes. The intestinal microbiota influences the pulmonary one and also the immune response. In acute respiratory infection, a dysbiotic state occurs that increases the prevalence of bacteria and bacterial metabolites, such as short-chain fatty acids (SCFA)[17,18]. This effect is called 'gut-lung axis' which would explain why patients with SARS-CoV-2 pneumonia often present digestive symptoms[19].

In the pathophysiology of liver involvement, bile duct cells are known to play an important role in liver regeneration and in the immune response, like hepatocytes, they also express ACE2[10]. The ACE2 receptor expression in cholangiocytes is twenty times higher in hepatocytes (reaching 2.6%), very similar to that of alveolar type II cells. In contrast, Kupffer and endothelial cells of the liver do not express ACE2.

SARS-CoV-2 binds to ACE2 in the cholangiocytes which could produce direct damage to the bile duct. Hepatocytes would not be a target to the virus, at least not through ACE2[9,20]. SARS-CoV-2 would cause injury by increasing expression of ACE2, causing a compensatory proliferation of hepatocytes derived from bile duct epithelial cells[19].

Therefore, these hepatic alterations are not necessarily due to direct injury to the hepatocyte. They could also be caused by drugs (antibiotics, corticosteroids, and antivirals) or by the systemic inflammatory response induced by pneumonia[11,20].

In both the GI tract and the liver, the virus triggers a T-cell response that leads to its activation, differentiation, and production of cytokines associated with its strains[9], producing a cytokine storm manifested by an increased TH17 response and elevated cytotoxicity CD8+ T-cells.

Ischemic hypoxia secondary to respiratory failure would play a role in those patients with severe hepatocellular damage[10,21]. Postmortem biopsies of a SARS-CoV-2 patients show moderate microvesicular steatosis and mild portal and lobular activity, suggesting that it could have been caused by SARS-CoV-2 infection or by drugs (drug-induced liver injury)[21,22]. Another mechanism could be the reactivation of known or unknown pre-existing liver diseases. There are drugs that, for example, can reactivate the activity of the Hepatitis B virus. It is not entirely known whether SARS-CoV-2 can exacerbate previous cholestasic disease[21].

Fecal-oral transmission

Since SARS-CoV-2 has been detected in the GI tract, saliva, and urine[24], human-to-human transmission may occur by different modes: exposure to via respiratory secretions, aerosols, contaminated surfaces, and also through feces[23].

SARS-CoV-2 has been detected in the stool of up to 50% of patients. In many cases, this detection did not concur with the presense of digestive symptoms[10].

Xing[25] reported three pediatric patients with SARS-CoV-2 (only one of them had digestive symptoms), PCR was performed on both pharyngeal swabs and stools, observing viral clearance of 2 weeks in the respiratory tract and more than 4 weeks in the stool.

Another study from Hong Kong describing a cohort of 59 adult patients along with a systematic review and meta-analysis, SARS-CoV-2 was detected in 15.3% of stools, including patients without GI symptoms. In the systematic review, up to 48% of patients had stools with SARS-CoV-2 RNA during the disease[1].

The RNA persistence in stool was longer than in respiratory samples, appearing as early as 2-5 days from the onset of the disease and remaining positive for more than 3 weeks after onset. In these studies, between 70.3% and 82% of patients had SARS-CoV-2 RNA in stool with a negative respiratory sample[1,7,26]. The significance of this finding is not knowing if they are particles of a live virus or just fragments of RNA[1,27]. Patients treated with corticosteroids present longer stool positivity[27], and patients with diarrhea at the onset of the disease, had higher stool viral loads than those without it[1].

Base this description, some hospitals included nucleic acid testing of stool samples as a standard for suspending quarantine. This observation is relevant considering the possibility of viral dissemination in pre- and school age children[25].

Therefore, fecal-oral transmission should be con-

sidered independently of the presence of GI symptoms[7,9,10,14]. Efforts are needed to prevent viral dissemination by this route when attendance to daycare, preschool, and schools resume, especially in developing countries[25].

Gastrointestinal manifestations

The classic symptoms of SARS-CoV-2 are fever, cough, fatigue, myalgia, and dyspnea. Less than 10% of infected children develop GI symptoms. Fever is the most common symptom (92.8%) followed by cough (69.8%), dyspnea (34.5%), myalgia (27.7%), and headache (7.2%)[28]. Symptoms are not present in 10% of children, 44-50% have a fever, and 82% have history of close contact[2].

SARS-CoV-2 infection can cause gastritis and acute enteritis, characterized by vomiting, nausea, abdominal pain, and diarrhea[14], they present with variable frequency and time of onset. Loss of appetite may be caused by an inflammatory state, hypoxia, depression, or adverse reactions to therapeutic drugs[27]. Regarding the presentation of GI symptoms, there are no coexisting, conditioning, or previous states[10].

In adults, digestive symptoms have been reported in patients with SARS-CoV-2 in several series. The first positive SARS-CoV-2 case in the USA had history of nausea and vomiting on day 4 of disease onset and self-limiting diarrhea on day 6[29].

Pan[19] describes that 50% of patients present one or more digestive symptoms with 3% presenting only digestive symptoms. Jin reports gastrointestinal symptoms in 74 of 651 patients (11.4%)[14]; Nobel in New York reports up to 35% (97/278)[30] and Zili Zhou described up to 26%[31].

Luo conducted a study in Wuhan on 1,141 patients during a period of 7 weeks where 16% (183) presented only gastrointestinal symptoms. The most common symptoms included loss of appetite (98%), nausea (73%), and vomiting (65%), i.e. there were digestive symptoms in almost 2/3 of patients. Diarrhea occurred in 37% and abdominal pain in 25%[32].

In adults, these symptoms present variable frequencies in different group descriptions as loss of appetite (78.6%), vomiting (65%-4.9%), diarrhea (37%-34%- 24%, 8.1%, 6.1%, 3%-8%), and abdominal pain (25%-1.9%)[10,12,14,19,28,32]. Lu in a cohort of 171 children reported diarrhea in 8.8% and vomiting in 6.4% of patients[33].

In the systematic review conducted by Cheung where 60 studies and 4,243 patients from all over the world were analyzed, 18 studies reported prevalence of loss of appetite, 32 of nausea and vomiting, 58 of diarrhea, and 12 of abdominal pain. The cumulative prevalence of loss of appetite was 26.8%, nausea and vomiting 10.2%, diarrhea 12.5%, and abdominal pain/discomfort 9.2%[1].

Gastrointestinal symptoms vary widely during the course of the disease. There were differences in symptom frequency between adults and children. Loss of appetite was the most common digestive symptom in adults (39.9%-50.2%), while diarrhea was the most common among children and adults (2%-49.5%). Vomiting was more common in children 3.6%-15.9% vs 6.5%-66.7% in adults. Gastrointestinal bleeding was present in 4%-13.7%. This study highlights abdominal pain as the most common symptom among critically ill patients (2.2%-6.0%)[27].

In Chile, according to the epidemiology department of the Ministry of Health, with data as of July 14, 2020, of 200,000 cases, 16.3% presented diarrhea and 9.5% abdominal pain.

Diarrhea is the most common digestive symptom. In up 34,3% of cases, it is liquid and presents as the initial symptom. It occurs most frequently 1 to 8 days after the onset of the disease with a median of 3.3 days[10,33] and is described as having low-volume, not been clinical severe, usually up to three stools per day[19,27]. It has an average duration of 4 days (3-6 days), and generally is self-limiting[14]. The management strategy is the usual one, emphasizing hydration[27].

When analyzing cases in adults with and without gastrointestinal symptoms, no significant statistical differences were found regarding demographic characteristics (age, sex, race, ethnicity, BMI, regional location) or in clinical evolution, however, of those who presented with gastrointestinal symptoms, only 11% of the total presented digestive symptoms at admission while the rest developed symptoms during hospitalization[10,30] Gastrointestinal symptoms seemed to be more frequent in families with SARS-CoV-2[14].

Since April 2020 cases of children with history of exposure to SARS-CoV-2 and multisystem inflammatory syndrome, characterized by a clinical signs of toxic shock or atypical Kawasaki syndrome have been reported in the United Kingdomi. Abdominal pain and gastrointestinal symptoms (vomiting, diarrhea) have also been described as common features of this new clinical syndrome[34].

Endoscopy and Proctoscopy

It is not very common to perform endoscopic procedures in these patients, endoscopy is generally relatively normal[15]. Lin reported a case of upper gastrointestinal bleeding where upper endoscopy showed multiple erosions and ulcers covered by white fibrin and clots in the lower third of the esophagus, SARS-CoV-2 was detected in this area, and biopsies showed presence of the virus in the stomach, duodenum, and rectum[35].

Routine endoscopic procedures should be avoided as they generate aerosols, especially in children where airway management is required, and endoscopy is generally performed on intubated patients[9].

Histology shows occasional lymphocytic infiltration in the esophageal squamous epithelium, abundant plasma infiltration, and lymphocytes with interstitial edema in the stomach, duodenum, and lamina propria of the rectum[27].

Electron microscopy, showed viral particles (60-90 nm) in the ileum and colon, located on the apical cells surface and rarely in glandular cells. They are located especially on the villous surface. At the cellular level, the virus is located in vesicles within the endoplasmic reticulum. There possibly is viral liberation from the apical membrane of enterocytes, but there is minimal disruption of intestinal cells by the virus despite the tropism. There is no evidence of villous atrophy despite viral adhesion and colonization[15].

Liver manifestations

A varying degree of alterations in liver function has been described[10,20]. Transaminases levels are commonly elevated, occurring up to 40%-60% of patients with severe disease compared with those who are asymptomatic or with mild disease, where it rises in 18%-25% of cases[10,11,36]. Increased transaminases are more frequently present in males[21].

This elevation often appears along with elevated creatine kinase (CK) and lactate dehydrogenase (LDH)[9]. The concomitant increase of CK and LDH suggests that viral myositis affected the elevation of glutamate oxaloacetate transaminase (GOT).

The number of patients with increased glutamate pyruvate transaminase (GPT) and GOT is significantly higher in patients with digestive symptoms suggesting that different degrees of liver damage occur in these patients[19,31].

Bilirubin levels are doubled in severe infection in up to 10%-53% of patients[10,21] this is probably related to self-reacting T-cells caused by virus and the cytokine storm[9].

The cholestatic pattern is rarely seen and many reports suggest that alkaline phosphatase is normal[10]. Albumin is low in severe cases and is a marker of poor prognosis[21]. In patients who have died due to SARS-CoV-2, the incidence of liver injury is as high as 58%-78%[11], however, severe liver dysfunction is rare.

Liver damage should be carefully monitored since increases of GPT and coexisting conditions have been observed in COVID-19 patients with gastrointestinal symptoms[14]. All children with SARS-CoV-2 and persistently elevated transaminases should be examined for other causes of liver disease, and if asymptomatic or have mild symptoms, they should not be hospitalized[9]. It is recommended that patients with newly diagnosed jaundice, GOT/GPT > 500 IU/L, or recently initiated hepatic decompensation should be hospitalized. Moderately increased transaminases in SARS-CoV-2 disease are not a contraindication for antiviral therapy, but require regular monitoring of liver function[11].

Is there an association between digestive symptoms and clinical severity?

In a systematic review, 17.6% of patients presented gastrointestinal symptoms, of those 11.8% had non-severe COVID-19, and 17.1% had severe COVID-19. Subgroup analysis shows that the presence of gastrointestinal symptoms was associated with a more severe disease course[1], especially the presence of abdominal pain.

Can we speak about risk factors for predicting severe/critical COVID-19 patients with digestive symptoms?

Some descriptions are inconclusive and that differ greatly from each other. Pan's group in China noted that the severity of the disease was greater when there were more pronounced digestive symptoms. One possibility is that digestive symptoms indicate increased viral load and replication within the gastrointestinal tract, and the other one is that there may have been delay in seeking medical evaluation, since there were no respiratory symptoms[19].

The presence of gastrointestinal symptoms was associated with an increased risk of up to 70% of testing positive for SARS-CoV-2 and having a longer duration of the disease (up to one week longer compared to patients without digestive symptoms)[30]. There was a longer hospital stay and greater liver involvement, including longer clotting time and higher liver enzyme elevation, compared with patients without digestive symptoms.

As the severity of disease increases, digestive symptoms worsen, however, there were no significant differences in mortality[14,19].

Final comment

According to the literature we reviewed, digestive and hepatic symptoms are clearly present in patients infected with SARS-CoV-2. The virus coexists in the gastrointestinal and respiratory tracts but persists lon-

ger in the digestive tract. There is no absolute certainty about the prognostic significance of these findings.

However, the significance of gastrointestinal symptoms should not be underestimated. It is important and urgent to be able to recognize the clinical spectrum of this disease. Specifically, the recognition of digestive symptoms and potential fecal-oral transmission that may influence the spread of the disease. Early recognition will allow early identification, triage, and proper isolation. Disinfection and proper stool management are crucial in endemic regions.

This review and recommendations have been developed based on currently available information. There are still more questions than answers regarding SARS-CoV-2, therefore, we need to act on the evidence we have.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

References

1. Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis. Gastroenterology. 2020. (20) doi: https://doi.org/10.1053/j.gastro.2020.03.065.
2. Zimmermann P, Curtis N, Coronavirus Infections in Children Including COVID-19 An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. Pediatr Infect Dis J 2020;39:355-68.
3. Ding S, Liang TJ. Is SARS-CoV-2 Also an Enteric Pathogen with Potential Fecal-Oral Transmission: A COVID-19 Virological and Clinical Review. Gastroenterology. 2020. https://doi.org/10.1053/j.gastro.2020.04.052.
4. Murray KF, Gold BD, Shamir R, et al. COVID-19 and the Pediatric Gastroenterologist. J Pediatr Gastroenterol Nutr. 2020 Publish Ahead of Print DOI : 10.1097/MPG.0000000000002730.
5. Coronavirus disease (COVID-19) Situation Report-103 Data as received by WHO from national authorities by 10:00 CEST. Julio 2020.
6. Departamento de Estadística al e Información de Salud. División de planificación sanitaria. Subsecretaría de Salud Pública. Cifras oficiales COVID-19 Chile al 14/07/2020. Encuesta nacional de Rama de Intensivo Pediátrico de SOCHIPE.
7. Sultan S, Lim JK, Altayar O, et al. AGA Institute Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. Gastroenterology. 2020. https://doi.org/10.1053/j.gastro.2020.03.072.
8. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics. DOI: 10.1542/peds.2020-0702.
9. Matthai J, Shanmugam N, Sobhan P. Indian Society Of Pediatric Gastroenterology HpAN, Pediatrics PGCOIAO. Coronavirus Disease (COVID-19) and the Gastrointestinal System in Children. Indian Pediatr. 2020.
10. Agarwal A, Chen A, Ravindran N. Gastrointestinal and Liver Manifestations of COVID-19. Journal Of Clinical And Experimental Hepatology https://doi.org/10.1016/j.jceh.2020.03.001.
11. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004.
12. García-Salido A. Revisión Narrativa Sobre La Respuesta Inmunitaria Frente A Coronavirus: Descripción General, Aplicabilidad Para Sars-Cov2 E Implicaciones Terapeúticas, Anales de Pediatria (2020). https://doi.org/10.1016/j.anpedi.2020.04.016.
13. Pirola CJ, Sookoian S. COVID-19 and ACE2 in the liver and gastrointestinal tract: Putative biological explanations of sexual dimorphism, Gastroenterology (2020), doi: https:// doi.org/10.1053/j.gastro.2020.04.050.
14. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020. doi:10.1136/gutjnl-2020-320926.
15. Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology. 2003;125(4):1011-7.
16. Perlot T, Penninger JM. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. Microbes Infect. 2013;15(13):866-73.
17. Marsland B,Trompette A,The Gut–Lung Axis in Respiratory Disease, Ann Am Thorac Soc 2015; 12 (2):S150-6.
18. Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The role of the lung microbiota and the gut-lung axis in respiratory infectious diseases. Cellular Microbiology. 2018;20:e12966. https://doi.org/10.1111/cmi.12966.
19. Pan L, Mu M, Yang P, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 2020;115(5):766-73. https://doi.org/10.14309/ajg.0000000000000620.
20. Chai X, Hu L, Zhang. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection, https://doi.org/10.1101/2020.02.03.931766.
21. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int. 2020 .doi: 10.1111/LIV.14470.
22. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. https://doi.org/10.1016/ S2213-2600(20)30076-X.
23. Homan M, Athiana I, Bontems P, et al. Gastrointestinal endoscopy in children and COVID 19 pandemic- ESPGHAN endoscopy SIG statement. 2020.
24. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.DOI: 10.1056/NEJMoa2002032.
25. Xing YH, Ni W, Wu Q, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J Microbiol Immunol Infect. 2020. https://doi.org/10.1016/j.jmii.2020.03.021.
26. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26(4):502-5. doi.org/10.1038/s41591-020-0817-4.

27. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther*. 2020;51:843-51. https://doi.org/10.1111/apt.15731.
28. Hormati A, Shahhamzeh A, Afifian M, Khodadust F, Ahmadpour S. Can COVID-19 present unusual GI symptoms? J Microbiol Immunol Infect. 2020. https://doi.org/10.1016/j.jmii.2020.03.020.
29. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929-36. DOI: 10.1056/NEJMoa2001191.
30. Nobel YR, Phipps M, Zucker J, et al. Gastrointestinal Symptoms and COVID-19: Case-Control Study from the United States. Gastroenterology. 2020. doi: https://doi.org/10.1053/j.gastro.2020.04.017.
31. Zhou Z, Zhao N, Shu Y, Han S, Chen B, Shu X. Effect of gastrointestinal symptoms on patients infected with COVID-19, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.03.020.
32. Don't Overlook Digestive Symptoms in Patients With 2019 Novel Coronavirus Disease (COVID-19) Shihua Luo, Xiaochun Zhang, and Haibo Xu Department of Radiology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, China Clinical Gastroenterology and Hepatology 2020 https://doi.org/10.1016/j.cgh.2020.03.043.
33. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663-5.
34. Mahase E, Covid-19: concerns grow over inflammatory syndrome emerging in children.BMJ 2020;369:m1710 .doi: 10.1136/bmj.m1710.
35. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020. doi:10.1136/gutjnl-2020-321013.
36. Guan GW, Gao L, Wang JW, et al. [Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia]. Zhonghua Gan Zang Bing Za Zhi. 2020;28(2):E002. PMID: 32077659. DOI: 10.3760/cma.j.issn.1007-3418.2020.02.002.